REMARKS/ARGUMENTS

The Status of the Claims.

Claims 1-13 and claim 16 are pending. Claims 1 and 16 are amended herein. No claims are added or cancelled herein. Claims 14 and 15 have previously been cancelled and claim 16 has previously been added. These amendments introduce no new matter and support is replete throughout the specification. These amendments are made without prejudice and are not to be construed as abandonment of the previously claimed subject matter or agreement with any objection or rejection of record.

With respect to claims 1 and 16, support for cells comprising the listed components can be found throughout the specification. The present amendments do not change the scope of the claims but are added to further clarify, e.g., that the cognate receptor, estrogen receptor, fos, jun and the promoter can not be considered to be the nuclear transcription factor ligand of the claims.

Applicants submit that no new matter has been added to the application by way of the above Amendment. Accordingly, entry of the Amendment is respectfully requested.

Interview Summary

Applicants appreciate the Interview of October 17, 2006, provided with Examiner Pak and SPE Nickol. Claims discussed included independent claims 1 and 16. Prior art discussed included U.S. patent 5,723,291 to Kushner ('291).

Examiner Pak pointed to some possible confusion concerning the phrasing of what the cells of the claims comprise in the absence of the nuclear transcription factor ligand.

Applicants noted that the present Action only acknowledges the absence of cognate receptor descriptions in the primary reference '291. However, Applicants noted there are several other limitations not addressed in the Action. Ultimately, the Office was unable to identify a reference, or combination of references, providing, e.g., 1) contacting a cell with the transcription factor ligand which is to a cognate receptor that is not an estrogen receptor and also contacting the cell with a compound having AP-1 mediated estrogenic activity, or 2) comparing expression of the reporter gene in the presence of the transcription factor ligand to

expression of the reporter gene in the absence of the transcription factor ligand, wherein a difference in expression indicates that the transcription factor ligand modulates estrogen activation at an AP-1 site.

35 U.S.C. §103(a).

Claims 1-13 and 16 were rejected under 35 U.S.C. §103(a) as allegedly obvious based on Kushner in light of Pfahl, Evans, Gaub, Webb, and Kushner (WO95/06754). Applicants traverse. Applicants stand by their remarks of previous Responses and include additional arguments, herein.

Three requirements must be met for a *prima facie* case of obviousness. First, the prior art reference must teach all of the limitations of the claims. M.P.E.P § 2143.03. Second, there must be a motivation to modify the reference or combine the teachings to produce the claimed invention. M.P.E.P. § 2143.01. Third, a reasonable expectation of success is required. M.P.E.P. § 2143.02. The teaching or suggestion to combine and the expectation of success must be both found in the prior art and not based on Applicants' disclosure. M.P.E.P. §2143. That is, a *prima facie* case of obviousness requires that the combination of the cited art, taken with the general knowledge in the field, must provide all of the elements of the claimed invention. When a rejection depends on a combination of prior art references, there must be some teaching, suggestion or motivation to combine the references. *In re Geiger*, 815 USPQ2s 1276, 1278 (Fed. Cir. 1987). Moreover, to support an obviousness rejection the cited references must additionally provide a reasonable expectation of success. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991), citing *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).

According to 37 CFR 1.104(c)(2) Nature of examination, "[w]hen a reference is complex or shows or describes inventions other than that claimed by the applicant, the particular part relied on must be designated as nearly as practicable. The pertinence of each reference, if not apparent, must be clearly explained and each rejected claim specified." Here, the issues are complex, and Applicants have previously requested a clear and concise explanation of the rejections. However, the rejections continue to reject the claims in bulk with discussion of the cited references separately. The rejection does not particularize, e.g., separately and particularly where each limitation of each claim can be found and what

particular combination of references provides the basis for the rejection. This failure of the Actions deprives the Applicant's of reasonable notice of the nature of the rejections and unreasonably increases the effort required to prepare a Response. Because the Actions are non-responsive to issues raised (as discussed below) and fail to provide adequate notice of the rationale for the rejections, Applicants request the present Action not be considered a final Office Action until such deficiencies are corrected.

Cited references do not teach all limitations of the claims.

As a preliminary matter, the basic premise of the continued rejections in this case is that Kushner '291 teaches all limitations of the present claims but for "a cognate receptor which is not [sic] estrogen receptor." See the Action at the top of page 6. All following analyses in the rejections of Action depend on this faulty premise.

Kushner '291 describes, e.g., a cell with an estrogen receptor that in the presence of estrogen can activate an AP-1 site (through fos and jun) that regulates expression of a first reporter gene. However, the present application essentially teaches and claims, e.g., methods of screening for non-estrogen ligands to non-estrogen receptors that can influence the expression of the reporter in the Kushner '291 cell.

Claim 1, for example, is as follows:

> 1. A method of screening a nuclear transcription factor ligand for an ability to modulate estrogen activation at an AP-1 site, said method comprising the steps of:
> a) providing a first cell, that even in the absence of said nuclear transcription factor ligand still comprises:
> a cognate receptor for the nuclear transcription factor ligand, which cognate receptor is not an estrogen receptor;
> an estrogen receptor;
> fos;
> jun; and,
> a promoter comprising an AP-1 site that regulates expression of a first reporter gene;
> b) contacting said first cell with said transcription factor ligand and with a compound having AP-1 mediated estrogenic activity; and,
> c) detecting expression of said first reporter gene, as compared to expression of said first reporter gene in the absence of said transcription factor ligand, wherein a difference in expression of said first reporter gene in the presence and absence of said transcription factor ligand indicates that said nuclear transcription factor ligand modulates estrogen activation at an AP-1 site.

Kushner '291 taught a system for detecting the presence of ligands that activate the estrogen receptor. The present method can essentially start with aspects of the Kushner '291 system, e.g., as a reference assay, but further includes additional novel components and interactions, e.g., a cognate receptor, contacting the cell with a compound and ligand, and detecting a difference between cell signals with and without the ligand. Kushner '291 can provide at most only the reference assay. All other components and interactions of the currently claimed methods were not present in Kushner '291. These new aspects include at least 1) a cognate receptor that is not an estrogen receptor; 2) the cognate receptor being for a nuclear transcription factor ligand that is not one of the other listed components of the cell; 3) contacting the cell with the transcription factor ligand which is to a cognate receptor that is not an estrogen receptor and also contacting the cell with a compound having AP-1 mediated estrogenic activity; and, 4) comparing expression of the reporter gene in the presence of the transcription factor ligand to expression of the reporter gene in the absence of the transcription factor ligand, wherein a difference in expression indicates that the transcription factor ligand modulates estrogen activation at an AP-1 site. None of these limitations are found in Kushner. All were discussed in the Response to the previous Office Action. Yet the present Action addresses only limitation 1, thus failing to made a *prima facie* case.

1) A cognate receptor that is not an estrogen receptor. The present Action acknowledges that Kushner did not describe a receptor, other than an estrogen receptor.

Applicants do not argue that in the universe there is not a receptor that is not an estrogen receptor. However, Applicants note that the particular "cognate receptor" of the invention, must be the cognate receptor for the nuclear transcription factor ligand (NTFL) of the claimed methods.

2) A cognate receptor for a nuclear transcription factor ligand that even when it is absent, the other listed system components are present in the cell. The action continues to suggest this limitation is present in Kushner '291. Applicants request, again, identification of where this limitation can allegedly be found in Kushner. Such identification is not present in the allegations of the Kushner teachings running from page 2 to 3 of the Action.

Applicants appreciate that the present Action, at the bottom of page 5, attempts to address the issue of the claim limitation "a cognate receptor for the nuclear transcription factor ligand, which cognate receptor is not an estrogen receptor". However, the conclusory statement "the combination of the references provide the cognate receptor for a transcription factor ligand which is not estrogen receptor" provides no substance. Where, in any cited reference can this receptor be found, e.g., in the cell, as claimed?

3) Contacting the cell with the nuclear transcription factor ligand which is to a cognate receptor that is not an estrogen receptor and with a compound having AP-1 mediated estrogenic activity. Nowhere in the Action is there an allegation that any of the cited references (or any combination of the references) teach this contacting limitation. This, even though identification of this limitation has been requested in many prior Responses to Actions. A *prima facie* case has not been made.

Applicants acknowledge that in the history of the art a cell has been contacted with a ligand to a receptor. Applicants acknowledge a cell has been contacted with putative ligands to screen for possible direct effects on a complimentary target receptor (e.g., see Kushner '291). However, the subject matter of the present claims is different in structure, function and kind. Prior art references teach contacting a cell with one ligand at a time and observing the direct effects on single receptor. However, no reference teaches contacting the cell of the claim with two ligands, much less the particular combination of an NTFL and a compound having AP-1 mediated estrogenic activity, as claimed. Of course, this limitation is not present in Kushner '291, contrary to the arguments of the present Action.

4) Comparing expression of the reporter gene in the presence of the transcription factor ligand to expression of the reporter gene in the absence of the transcription factor ligand, wherein a difference in expression indicates that the transcription factor ligand modulates estrogen activation at an AP-1 site. Nowhere in the Action is there an allegation that any of the cited references (or any combination of the references) teach this comparing limitation. This, even though identification of this limitation has been requested in many prior Responses to Actions. A *prima facie* case has not been made.

Applicants acknowledge that expression of a reporter gene has been compared in the presence and absence of a ligand. However, the present limitation includes additional aspects and is qualitatively different from cited references. The present invention is not merely the combination of two ligand/receptor/reporter systems, as the Action may be suggesting. In claim 1, modulation of an AP-1 site activation level (e.g., established by contacting estrogen to a cell having an estrogen receptor) can be detected in response to contact with a non-estrogenic ligand. No reference teaches detection of a change in a first ligand/receptor/reporter system resulting from the presence or absence of a different ligand to a different receptor. Such a concept is not present in any cited reference, and can not simply result from a combination of two direct reporting schemes (i.e., the claims are not obvious according to *In re Kerkhoven*). Of course, no reference, or combination of references, can teach the more particular claimed embodiments specifically involving, e.g., estrogen receptors, compounds having AP-1 mediated estrogenic activity, and NTFLs to another receptor that is not an estrogen receptor. Again, the Action is incorrect in suggesting this limitation is found in Kushner '291.

Because several limitations of the independent claims 1 and 16 are not taught in the cited references, Applicants respectfully request withdrawal of the rejections under section 103. As dependent claims include the limitations of the claims upon which they are dependent, they too are not obvious.

Additional limitations of dependent claims are not found in the cited references. Although claims 2 and 3 are rejected, Applicants can find no reference to the subject matter of these claims in the present Action (therefore, there is not *prima facie* case for their rejection). In previous Actions the claims were apparently rejected based on the statement that they do not further limit rejected claim 1. However, as stated in the previous Response (and not contested in the present Action), claims 2 and 3 include limitations not found in claim 1 and therefore are further limiting. Moreover, claims 2 and 3 include limitations not found in the cited references, such as, e.g., a second cell comprising the cognate receptor for the nuclear transcription factor (not necessarily comprised in the first cell), or the limitation of contacting the second cell with the nuclear transcription factor ligand, or the limitation of detecting expression of a second reporter gene. With regard to

claim 3, the cited references fail to provide the limitation wherein the first and second cell are the same cell. These limitations are not described in the cited references and not identified in the present Action.

Without addressing Applicant's remarks on the subject from the previous Response, the present Action apparently rejects claims 4 and 5 again because they do "not further limit claim than the receptor in claims 2 and 3." Applicant again can not elucidate the basis for this statement from reading the Action. Applicant again notes, however, that claims 4 and 5 include limitations not required by claim 1 and not found in the cited art. Claims 4 and 5 also contain limitations different from those of claims 2 and 3, and have a scope different from claims 2 and 3. For example, the additional limitations of claims 4 and 5 over claim 1 include at least a second cell comprising a cognate receptor of the transcription factor ligand (which is not necessarily comprised in the first cell), a response element that regulates a second reporter gene, contacting the second cell with the transcription factor ligand, and detecting the second reporter gene. With regard to claim 5, the cited references additionally fail to provide the limitation wherein the first and second cell are the same cell. This contrasts with claim 2, which provides a second cell comprising the cognate receptor of claim 1 (which is not an estrogen receptor) and an estrogen response element, these limitations are not found in claim 4. It is not fair to continue with a line of rejection without addressing, and logically responding to the remarks going back over several Responses to previous Actions. The limitations of claims 2 to 5 are not present in the cited references, so there are further reasons the claims are not obvious in light of the cited references.

Because the stated basis of the Action for rejection is the allegation that only one limitation of the claims is not found in Kushner, the Action is clearly in error. Because the Action does not identify disclosure in other cited references to allegedly teach any of the several limitations not found in Kushner, a *prima facie* case has not been made the rejections must be withdrawn.

The limitations are not found in other cited references.

None of the secondary references of Pfahl, Evans, Gaub, Webb, and Kushner provide the claim limitations missing from Kushner '291. No combination of the cited references can provide all the limitations missing from Kushner '291.

Evans '592 describes a cell containing a hormone receptor that controls expression of a reporter through AP-1 proteins at an AP-1 site: essentially the classic AP-1 mediated reporter system common to several cited references. In the case where the hormone receptor is an estrogen receptor, Evans describes essentially the assay system of Kushner '291. Evans also describes cells containing certain receptors that are not estrogen receptors, such as a glucocorticoid receptor. However, Evans does not describe at least the limitations 2, 3 and 4. Evans does not describe contacting a cell with the transcription factor ligand which is to a cognate receptor that is not an estrogen receptor and also contacting the cell with a compound having AP-1 mediated estrogenic activity. Although estrogen receptors are mentioned in a list of Evans, estrogen and compounds with AP-1 mediated estrogenic activity are not. Moreover, Evans does not teach contacting the cell with a transcription factor ligand to the cognate receptor that is not an estrogen receptor, because Evans' test compounds all appear to be transfected receptor proteins, i.e., transcription factors, typically are not considered transcription factor ligands. In addition, Evans does not discuss comparing expression of the reporter gene in the presence of the transcription factor ligand to expression of the reporter gene in the absence of the transcription factor ligand, wherein a difference in expression indicates that the transcription factor ligand modulates estrogen activation at an AP-1 site. Evans only describes a simple system of a receptor and AP-1 reporter. Evans does not provide the claim limitations discussed above as not provided by Kushner '291.

Moreover, Evans fails to disclose at least the additional limitations of several dependent claims, such as, e.g., the second cell with an ERE and the cognate receptor of claim 2; a cell with an ERE and the cognate receptor of claim 3; the second cell of claim 4; the cell of claim 5, e.g., with a cognate receptor and a second reporter; a factor ligand to a cognate receptor of claim 6; or, a progestin cognate receptor of claim 12.

Pfahl describes "a method of inhibiting the transcription of a gene, which is activated by AP-1 or an AP-1 component, comprising binding AP-1 or the component with a nuclear receptor so as to prevent the binding of AP-1 to the gene." See abstract.

As a preliminary matter, the Action identifies dexamethasone as a compound having AP-1 mediated estrogenic activity. First, dexamethasone is not discussed in Pfahl. Second

the interpretation of dexamethasone as a compound with estrogenic activity requires an unreasonable and overly broad reading of the statement in the present specification at the top of page 8 : "'a compound having AP-1 mediated estrogenic activity' refers to a compound that, when present in a cell containing a gene under control of an AP-1 site and AP-1 proteins, activates transcription of the gene under control of the AP-1 site." The final clause of the sentence can not be used to remove the fact that the compound at the beginning of the sentence has estrogenic activity. The statement must be read (in light of common usage of estrogenic activity and the present specification) to mean "an estrogenic compound", not to mean "any compound". For example, see the specification at page 11, line 13; page 13, line 5; page 13, line 16; and page 22, line 6. Interpretation of compound having AP-1 mediated estrogenic activity to include any compound having AP-1 mediated activity is inappropriate usage which is not a basis, e.g., to deem dexamethasone to be an estrogen. Moreover, in the Evans reference, dexamethasone activates the glucocorticoid receptor, which inhibits the signal from the phorbol activated reporter system. This can not be considered estrogenic activity. Contrary to the statements in the Action, Pfahl does not teach contacting with a compound having AP-1 mediated estrogenic activity.

Pfahl does not describe at least the limitations 2, 3 and 4 of claims 1 and 16. From Applicant's review of the Pfahl system, it fails at least to disclose: a method of screening for nuclear transcription ligands; a method in which estrogen activation of an AP-1 site is modulated by a ligand to a cognate receptor which is not an estrogen receptor; contacting a cell with both a ligand to the cognate receptor and a compound having estrogen mediated estrogenic activity; and detecting expression of the reporter gene to determine any modulation of the ligand on estrogen activation of the AP-1 site. Although Applicants have previously specifically requested identification of where these limitations are allegedly present in Pfahl, the present Action makes no attempt to address these issues.

With regard to dependent claims, Pfahl does not describe: the second cell with an ERE and the cognate receptor of claim 2; a cell with an ERE and the cognate receptor of claim 3; the second cell of claim 4; the cell of with a cognate receptor and a second reporter of claim 5; an estrogen receptor expressed from a heterologous DNA of claim 8; a cell

expressing fos or jun from a heterologous DNA of claim 10; or, a progestin cognate receptor of claim 12. Identification of these limitations in the reference was requested and denied.

. **Gaub**, as cited on page 1271, provides cells comprising an estrogen receptor and estradiol inducing transcription of a reporter gene through fos and jun at an estrogen responsive element (ERE), e.g., in the presence of a phorbol ester. Gaub fails to provide many of the same limitations not found in Kushner, Evans or Pfahl, as discussed above, such as at least limitations 2, 3 and 4. On page 4 of the Action, no attempt is made to identify where these limitations can be found, but the erroneous line of reasoning continues deeming all compounds activating AP-1 to be "estrogenic". Gaub fails to provide a method of screening a nuclear transcription factor ligand to a cognate receptor (which is not an estrogen receptor) for an ability to modulate estrogen activation at an AP-1 site. Gaub further fails to describe at least, e.g., a cognate receptor for a transcription factor ligand that is not listed as comprised in the cell and which is not an estrogen receptor; contacting the cell with the transcription factor ligand to the cognate receptor; comparing expression of the reporter gene in the presence and absence of the transcription factor ligand; a second cell comprising the cognate receptor for the nuclear transcription factor (absent from the first cell); contacting the second cell with the nuclear transcription factor ligand; detecting expression of a second reporter gene; or expression of two different reporter genes in the same individual cell.

The final Webb and Kushner references are acknowledged as cumulative to Kushner '291 and provide no additional limitations. The rejections of all claims based on alleged obviousness should be withdrawn for failure of the combined references to describe all the limitations of the claims.

An accounting to the limitations not found in Kushner and also not found in the cited references shows that there is no combination of cited references that can possibly provide at least the limitations 3 and 4. Therefore, the rejections must be withdrawn.

Combinations of Kushner with cited references are not motivated.

Assuming arguendo that the cited references could be combined to provide the present claims. Such combinations are not motivated and therefore the claims are redundantly non-obvious.

As a preliminary matter, Applicants believe the cited motivation of Evans is misstated. The Action at page 5 suggests that because understanding regulatory effects of hormones is desirable, motivation can be found for combining the cited references. First, this misreads the facts of Evans. In columns 1 and 2, Evans states that those in the art had previously been unmotivated to study modulation of a regulatory protein because there "is a strong likelihood that an undesirable side effect will occur". Evans states the concern was "it would not be possible to alter the regulatory effect of a given protein without also altering some other regulatory effects of that protein." Emphasis added. Evans may have been suggesting that his new methods can help address problems involved in modulation of a single regulatory protein, but this does not provide a motivation, e.g., to study the even more complicated multiple receptor systems of the claimed methods. Second, the cited motivation misreads the law. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). Although Evans may find it desirable to study regulatory effects of a protein, it does not suggest the desirability of the combination suggested in the Action (which we have noted does not describe the present invention).

Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See, *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). Here, there is not a suggestion in any of the references to make a combination that provides the claimed inventions. In fact, no express or implicit teaching or motivation can exist to combine references forming an invention when the references themselves do not cumulatively include all the necessary limitations of the invention.

Evans is cited, at columns 1 and 2, as motivating the present inventions. However, Evans teaches competitive interactions of recombinant proteins in a cell and directs one to the study of interactions between various receptor proteins and not the screening of ligands, or the present invention. This mis-motivation is only accentuated by the further cited alleged

motivation of Gaub, which again, is focused on receptor protein interactions and interactions with nucleic acids, but not screening or interactions with ligands. Pfahl suggests his methods can be useful in screening for new ligands, at the top of column 2. However, such screening methods are never described. Pfahl teaches away from the present invention by directing the poisoning of the system and making the present methods non-functional, e.g., by application of phorbol esters. Again, there can be no motivation in a combination that does not provide all the necessary limitations.

If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims prima facie obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959). Assuming *arguendo* that the references could provide all the limitations of any rejected claim, the suggested modification to the primary reference (Kushner) would necessarily change the principle of operation substantially. The suggested changes to the estrogen detector of Kushner (patent '291) would require a substantial reconstruction and redesign of the assay system and a change in the basic principle under which the Kushner system was designed to operate. Kushner operates, e.g., by activating AP-1 proteins to promote translation of a reporter at an AP-1 site in the presence of estrogen. With theoretical modifications to provide claim 1, the system would have to change in operation, e.g., from a direct signal output assay to a new and different modulated signal output resulting from new interactions with additional (e.g., cognate) receptor systems. The changed system would operate to provide results unrelated to the assay results of the original Kushner '291 technique.

In the Action at page 6, it is argued that "the nature of progress in science is improvement upon previous inventions ... and ... references are well known in to one of ordinary skill in the art to use as motivation to add method steps." Therefore, the Action suggests the suggested combinations would <u>not</u> change the principle of operation of the primary reference. This statement is illogical. The suggested combinations remain unobvious based on *In re Ratti.*

There would be no expectation of success in the cited combinations. Combinations of cited art would not be expected to succeed in providing the presently

claimed inventions because they are missing critical limitations for the function of the screening methods. Furthermore, the presence of chemicals, such as phorbol esters found in many of the cited references, would create reporter signal noise rendering modulation by cognate receptors undiscernable or incapable of interpretation in the screening methods. In the Action at page 6, the examiner states that there is no proof that , e.g., phorbol esters would cause a background signal problem in the methods of the invention. Applicants reassert that such compounds would generate a signal in the systems that is non-specific to the reference (estrogenic) or test (NTFL) side of the mehtods. This non-specific signal is inherent in the compounds and proof of such signals is in the teachings of the cited references. The fact that there would be no expectation of success can not logically be brushed off with the statement "the state of the art is cumulative and analogous art is well known to one of ordinary skill in the art."

Because a *prima facie* case has not been made, all the limitations of the claims do not exist in the cited references, the cited combinations are unmotivated, and there is no expectation of success in the cited combinations, the rejections for alleged obviousness must be withdrawn.

Double Patenting.

Claims have been rejected based on the judicially created doctrine of obviousness-type double patenting. Applicants traverse.

Applicants note that the present claims can not be considered to involve obviousness type double patenting for the reasons discussed above with regard to the obviousness rejections based on Kushner '291.

An obviousness type double patenting rejection is appropriate if the claimed invention, while not identical, is not patentably distinct with respect to the claims of a prior patent in light of the prior art. A claimed invention is not patentably distinct if all of the claimed elements are found in one or more pieces of prior art, and if there is motivation to combine the prior art with a reasonable expectation of success. Because the claims are not obvious, as discussed above, they can not be subject to this double patenting rejection.

Kushner '291 includes, e.g., the following claim:

1. A method for screening a test compound known to have antiestrogenic activity for agonistic estrogenic activity mediated through an indirect estrogen response, the method comprising:

a) providing a cell comprising AP1 proteins, an estrogen receptor, and a construct comprising a promoter comprising an AP1 site which regulates expression of a reporter gene;

b) contacting said cell with said test compound known to have antiestrogenic activity; and

c) detecting the expression of said reporter gene wherein enhanced expression of said reporter gene indicates that said test compound has agonistic estrogenic activity mediated through an indirect estrogen response.

Claims 1-13 and 16 of the present invention relate to a method of screening a nuclear transcription factor ligand for the ability to modulate estrogen activation at an AP-1 site. The elements of the method are:

a) providing a first cell, in the absence of said nuclear transcription factor ligand, comprising:

a cognate receptor for the nuclear transcription factor ligand, which cognate receptor is not an estrogen receptor;

an estrogen receptor;

fos;

jun; and,

a promoter comprising an AP-1 site that regulates expression of a first reporter gene;

b) contacting said first cell with said transcription factor ligand and with a compound having AP-1 mediated estrogenic activity; and,

c) detecting expression of said first reporter gene, as compared to expression of said first reporter gene in the absence of said transcription factor ligand, wherein a difference in expression of said first reporter gene in the presence and absence of said transcription factor ligand indicates that said nuclear transcription factor ligand modulates estrogen activation at an AP-1 site.

The '291 patent relates to a different method for screening a different type of test compound involving providing a cell comprising: AP-1 proteins (e.g., fos and/or jun); an estrogen receptor; and, a construct comprising an AP1 site which regulates expression of a reporter gene. None of the claims of the '291 patent recites, e.g., a cell with both an estrogen receptor and a cognate receptor to an transcription factor ligand that is not fos or jun, or contacting the cell with both the transcription factor ligand to the cognate receptor and a compound having AP-1 mediated estrogenic activity, or comparing expression of a reporter gene in the presence and absence of transcription factor ligand, as is found in independent

claim 1 of the present invention. Additional limitations not found in the specification of the '291 patent, as discussed above, are also not present in the '291 claims.

The Examiner has not pointed to anything in the cited references that provides all the limitations missing from the rejected claims. Applicants have not found these limitations with reasonable efforts. The cited references cumulatively provide, e.g., individual hormone receptors that activate expression of a reporter gene through an AP-1 protein/receptor element pathway. As discussed above in the arguments against the obviousness rejections, no combination of the same cited references with Kushner '291 provides any of several limitations including, e.g., a method of screening a nuclear transcription factor ligand, which binds a cognate non-estrogen receptor to modulate estrogen activation of an AP-1 site; contacting a cell with both a ligand to a cognate receptor and a compound having AP-1 mediated estrogenic activity wherein the ligand modulates estrogen activation at an AP-1 site.

The present claims are patentably distinct from the '291 claims because many of the claimed elements are not found in the suggested combination of references. Furthermore, there is no motivation to combine the prior art with a reasonable expectation of success, as discussed above. Therefore, the rejection for alleged double patenting should be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the claims are deemed not to be in condition for allowance after consideration of this Response, a telephone interview with the Examiner is hereby requested. Please telephone the undersigned at (510) 769-3510 to schedule an interview.

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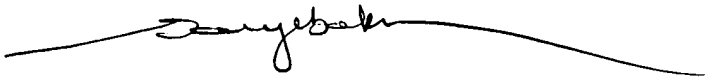
Respectfully submitted,



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Attachments:

1) A transmittal sheet;
2) A fee transmittal;
3) A petition for a 2-month extension;
4) A notice of Appeal; and,
5) A receipt indication postcard.